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Phase II study results on safety and efficacy of CAELYX® (DOXIL®) in combination with paclitaxel in the treatment of metastatic breast cancer

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The combination of doxorubicin and paclitaxel has produced encouraging response rates in the treatment of metastatic breast cancer. However, this regimen has considerable toxicities, in particular cardiac toxicity with high cumulative doses. CAELYX® is a doxorubicin formulation in which the drug is encapsulated within pegylated (STEALTH®) liposomes. The altered characteristics imparted by the encapsulation may reduce the risks of myelosuppression and cardiotoxicity in combination with paclitaxel. Forty three patients with confirmed metastatic cancer have been treated with paclitaxel and Caelyx to investigate the efficacy and toxicities of this combination. Patients were permitted up to 2 prior chemotherapy regimens which could have included prior anthracyline (16 pts) and/or taxane (3 pts). Median age 54.5 (range 73–31). The starting dose of CAELYX was 50 mg/m^2 every 6 weeks (n = 6), but was changed to 30 mg/m^2 every 3 weeks mg/m^2 (n = 37). Twenty five patients are currently evaluable for efficacy: 1 complete response, 14 partial responses, 3 stable disease, 7 progressive disease. (Five patients are not assessable for efficacy and 13 are too early for assessment) Twenty four patients have completed treatment with a median of 5 doses (range 1–10) of paclitaxel and 4 doses (range 1–8) of CAELYX was administered The most commonly observed toxicities were mucositis when Caelyx was given every 6 week, palmar-plantar erythrodysaesthesia (PPE) when Caelyx was given every 3 weeks and neutropenia. Accordingly dose reductions and delays were scheduled for >grade 2 PPE, myelosuppression or mucositis.. CAELYX doses were reduced in 13 patients and paclitaxel doses in 2 patients. Dose delays were required in 18 patients. Eighteen patients are still being treated of whom 11 have had dose delays and 2 reductions in the dose of Caelyx.

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A Phase II study of IncelTM (biricodar, VX-710) in combination with paclitaxel in women with advanced breast cancer refractory to paclitaxel

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IncelTM/VX-710 is a potent inhibitor of MDR mediated by P-glycoprotein and MRP expression. We conducted a Phase II study evaluating safety, tolerability and efficacy of Incel/paclitaxel (P) in breast cancer patients (pts) refractory to prior P therapy. Inclusion criteria: * 2 prior chemotherapy regimens for advanced disease, progressive disease on P, or relapse within 3 months of prior P therapy, ECOG performance status * 2; normal bilirubin, AST and ALT * 1.5 × ULN; baseline ANC and platelets * 1500 and 100,000, respectively. Pts received Incel (120 mg/m^2/hr) as a 24-hr infusion with 3-hr P at 80 mg/m^2 (P AUC and time > 0.05 mM comparable to 175 mg/m^2 P). The study enrolled 38 pts. Demographics, treatment, and safety data are available from 30 pts who received 76 treatment cycles. Demographics: median age 49 yr. (range 29 to 65 yr), 27/30 with ECOG performance status 0 or 1, prior treatment included adjuvant chemotherapy (18 pts), 2 prior regimens for advanced disease (17 pts), and P as initial therapy for advanced disease (13 pts). The majority of pts were resistant to initial P therapy. Incel/P has been well tolerated with myelosuppression as the principal treatment toxicity. Hematology data available for 34 cycles shows that median WBC and ANC nadirs for the first 2 cycles ranged from 2.1 to 2.6 × 103/mm3 and 0.5 to 0.70 × 103/mm3, respectively. Gr 3 or Gr 4 neutropenia was observed in 32% and 53% of cycles, respectively. Incel/P had no effect on platelet counts. Myelosuppression observed with Incel/P is similar to 24-hr P infusion. Non-hematological toxicities included: mild to moderate asthenia, fever, anemia, paresthesia, headache, nausea and myalgia. Analysis of P pharmacokinetics for 19 pts indicates a mean weight normalized CLs of 0.120 L/hr/kg and Vss of 1.65 L/hr/kg indicating P exposure is comparable to a 3-hr 175 mg/m^2 infusion. Thirty five pts are evaluable for response: 3 pts achieved PRs, 2 pts had minor responses (~30% shrinkage) and 5 pts are continuing therapy. These results suggest that Incel/P therapy can benefit some breast cancer pts with strictly defined P refractory disease, and provides a rationale for studies in pts with less advanced disease.

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Phase II trial of docetaxel and Herceptin (R) as first- or second-line chemotherapy for women with metastatic breast cancer whose tumours overexpress HER2

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Purpose: Women with metastatic breast cancer whose tumours overexpress HER2 have more aggressive disease and shortened survival. Herceptin (trastuzumab) as a single agent has shown activity in such patients and the addition of Herceptin to chemotherapy has improved the response rate and time to disease progression. Docetaxel is an active agent in the treatment of metastatic breast cancer and has shown response rates superior to that of doxorubicin.

Methods: This trial was the first to assess the safety and efficacy of combining Herceptin and docetaxel. The treatment regimen was docetaxel 75 mg/m^2 every 3 weeks for 6 cycles, with Herceptin initiated on day 1 as a 4 mg/kg loading dose followed by 2 mg/kg weekly until disease progression. Patients were premedicated with a standard 3-day dexamethasone regimen of 8 mg po bid. Herceptin was administered first, followed by a 1-hour docetaxel infusion. Eligibility criteria included: measurable metastatic breast cancer; 2+ or 3+ HER2 overexpression (DAKO kit); no prior taxoid therapy; less than or equal to one prior regimen for metastatic breast cancer; cumulative doxorubicin dose < 250 mg/m^2; and normal LVEF. Primary endpoints included: response rate; response duration; time to treatment failure; and safety/tolerability.

Results: To date, a total of 14 patients have received more than 50 cycles (range 1+ to 7+) of therapy. There have been 2 confirmed PRs, 3 minor responses and no reports of serious toxicities. One patient who was ineligible secondary to laboratory parameters was inadvertently enrolled and experienced an early death attributable to progressive disease.

Conclusions: These preliminary data indicate that the combination of docetaxel and Herceptin is well tolerated and accrual continues to a total of 30 patients. Further response data will be presented at the meeting.

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Phase I/II trial of oral UFT/Leucovorin (LV) and paclitaxel (P) in the second line treatment of patients (PTS) with metastatic breast cancer (MBC)

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Introduction: Phase II studies demonstrate efficacy and low toxicity for the continuous infusion of low dose 5-FU (Ann. Oncol. 7: 807–13, 1996) in pretreated pts with MBC. In our hands P in combination with weekly 5-FU/LV constitutes an active salvage regimen for pts with MBC (Ann. Onc. 9: 45–50, 1998). UFT/LV allows delivery of prolonged exposure to 5-FU without the need for central venous catheters or infusion pumps.

Patients and Methods: UFT, which is composed of 1-(2-tetrahydro-furyl)-5-FU (ftorafur) and uracil in a molar ratio of 1:4, was administered orally plus LV and in combination with P. Pts were treated as a part of an ongoing phase I/II protocol in order to determine the safety, activity and pharmacokinetics of this combination. After premedication, pts received a fixed dose of P 175 mg/m^2 3 h i.v. on day (d) 1 at all dose levels (dl). UFT was administered in combination with 90 mg/d of LV in three divided doses for 14 d's. The UFT dl's were dl1 300, dl2 400, dl3 500, dl4 600 and dl5 700 mg/d. The cycles were repeated every 21 d's. So far 26 pts entered the trial: 6 pts dl1, 5 pts dl2, 3 pts dl3, 6 pts dl4 and 6 pts dl5. All pts have had prior CTX either as an adjuvant, for MBC or in both settings.

Toxicity and Results: The main hematological toxicity (CTC grade III/IV) was neutropenia in 32%. CTC grade I/II toxicity including PNP, arthralgia and myalgia were common but not dose limiting Dose limiting toxicities (DLT) were: dl1–3: 14 pts (74 cycles) no DLT's; dl4: 6 pts (28 cycles) febrile neutropenia; dl5: 6 pts (20 cycles) diarrhea, nausea/vomiting, thrombopenia > 35 d. MTD was reached with dl5 and dl4 is used within the ongoing phase